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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In re application of:

BIRNSTIEL *et al.*

Appl. No.: 08/380,200

Filed: January 30, 1995

For: **New Protein-Polycation Conjugates**

Art Unit: 1816

Examiner: Eisenschenk, F.

Atty Docket: 0652.1080001/RWE/LBB

## *Reply Under 37 C.F.R. § 1.111*

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

In reply to the Office Action mailed October 28, 1997, a request for a three month Extension of Time and the requisite fee being filed herewith, Applicants request that the rejections be reconsidered in light of the following remarks.

### *I. Status of the Claims*

The claims being examined in this application are 1-20, 28-29, 32-34 and 36-40. It appears that the Examiner has overlooked claim 29 when indicating the rejected claims on the face page of the Office Action. Applicants assume that this was done in error and that the claims currently being examined are as indicated above.

### *II. Miscellaneous*

Applicants wish to thank the Examiner for the courtesy of the interview on October 8, 1997. Applicants note the Examiner's reference to this interview at page 2 of the Office Action.

In regard to this interview, Applicants further note the Examiner's reference to the selection of T-cell antibodies as targeting agents for T-cells in Hirsch (U.S. Patent No. 5,428,132 issued June 27, 1995 - hereinafter "Hirsch"). Applicants acknowledge the recitation in Hirsch at column 4, lines 47-48, that refers to "the antifection of the T-lymphocytes using an antibody against T-cells". This recitation, however, is directed to the use of such antibodies where the DNA is *directly* conjugated to said antibody. Contrary to Hirsch, the present invention involves a protein-polycation complex, not direct conjugation of an antibody to the DNA. As such, Hirsch fails to remedy any of the deficits in the art that the Applicants raised during the interview, as well as throughout the prosecution history of this application. Hirsch fails to motivate one of ordinary skill in the art to conjugate a T-cell antibody or targeting agent to a polycation and complex this conjugate with a nucleic acid. To do so, one would have to proceed contrary to the teachings of Hirsch.

## *III. Rejection of the Claims under 35 U.S.C. § 103*

### A. General Rebuttal of All Rejections under 35 U.S.C. § 103.

Before addressing the specifics of the rejections, Applicants respectfully direct the Examiner's attention to *Ex parte Obukowicz*, 27 U.S.P.Q.2d 1063 (BPAI 1993), a copy of which is enclosed. The following arguments are equally applicable to all § 103 rejections raised by the Examiner.

In *Obukowicz*, the Board of Patent Appeals and Interferences reversed an Examiner's rejection under § 103 that was based on a combination of references. In reversing the Examiner's rejection under 35 U.S.C. §103, the Board noted that "[w]e are unable to find a suggestion [in the art] *to do* what appellants have done. *Id* at 1065." The Board reviewed the art relied on by

the Examiner and dismissed one reference stating that it was "replete with advice" but contained "little information regarding how to use the transformed bacteria and clearly does not *specifically suggest* appellants' use." (Emphasis added). Applicants respectfully assert that the same could be said for the art cited in the above-captioned application. As in *Obukowicz*, none of the currently cited art is concerned with Applicants' invention, i.e. protein-polycation conjugates that are targeted to T-cells.

In *Obukowicz*, The Board continued:

> This specific statement regarding combating mosquitos using genetically engineered "natural pond microflora" is relied on by the examiner for the "suggestion" required by the aforementioned case law. However, the specific statement by Dean is not a suggestion to insert the gene into the *chromosome* of bacteria *and* apply that bacteria to the plant environment in order to protect the plant.

*Id* at 1965. Again, Applicants respectfully assert that a similar argument could be presented for the art cited in the present application. As in *Obukowicz*, none of the art contains the specific suggestion to obtain a protein-polycation conjugate comprising "a protein capable of binding to a cell surface protein other than the transferrin receptor expressed by cells of the T-cell lineage". Further, as in *Obukowicz*, the cited art gives at best, no more than general guidance and is not *specific* as to the particular form of the claimed invention or how to achieve it.

Applicants respectfully suggest that, as indicated in *Obukowicz* such general guidance may make an approach no more than obvious to try, however, it still fails to make the invention obvious because "obvious to try" is not the appropriate standard. See *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). As in *Obukowicz*, it is irrelevant that one can, in some embodiments, theoretically explain the technological rationale for the claimed invention

using *selected* teachings from the references. This approach has been repeatedly criticized as hindsight reconstruction.

Therefore, because the art does not suggest the particular form of the invention, and because the art does not specifically suggest that the artisan do what Applicants have done, Applicants respectfully assert that no motivation exists for combining the cited art and no *prima facie* obviousness has been established.

Additionally, throughout the rejections, e.g. at page 3, third full paragraph of the Office Action, the Examiner repeatedly bases the combination of applied art on what might have been "desired" by those of skill in the art. Merely because there may be a "desire" to obtain something, does not mean that there was sufficient motivation for combining the applied art. In fact, if as the Examiner contends, there really was a "desire" in the art to do what Applicants have done (but what had not actually been accomplished prior to Applicants' invention), it is respectfully suggested that this could be interpreted to be a long-felt, but unmet need. If this is the case, then the Examiner's basis for combining the art actually militates against the obviousness of the invention. This is because a "long-felt" but unmet need is one of the secondary criteria that can be considered when determining the non-obviousness of an invention (See *Graham v. John Deer Co.* 148 U.S.P.Q. (BNA) 459 (1966)). Accordingly, based on all of the above, the claimed invention was not obvious in view of the applied art and *all* rejections of the claims under 35 U.S.C. § 103 should be withdrawn.

**B. Claims 1-8, 11-20 and 36-40.**

At page 2 the Examiner has rejected of claims 1-8, 11-20 and 36-40 under 35 U.S.C.

§ 103 as allegedly being unpatentable over Wu *et al.*, U.S. Patent No. 5,166,320 (hereinafter Wu) or Wagner *et al.*, *Proc. Natl. Acad. Sci. USA 87*:3410-3414 (1990) (hereinafter Wagner) in view of Goers *et al.*, U.S. Patent No. 4,867,973 (hereinafter Goers) or Hirsch *et al.*, U.S. Patent No. 5,428,132 (hereinafter Hirsch), Carriere *et al.*, *Exp. Cell Res. 182*:114-128 (1989) (hereinafter Carriere), Knapp *et al.*, *Immunology Today 10*:253-258 (1989) (hereinafter Knapp) and Young *et al.*, *J. Immunol. 136*:4700 (hereinafter Young) or Weinberger *et al.*, *J. Cell. Biochem. Suppl. 8A*:184 (1984) (hereinafter Weinberger). Applicants respectfully traverse this rejection.

In the previous Office Action dated December 24, 1996, the Examiner rejected the same claims over Wu or Wagner in view of Goers or Hirsch, Carriere and Knapp. The argument previously made in the Response filed May 27, 1997 (beginning at page 2) to overcome this art is incorporated herein by reference. This argument can be summarized as being that there was no suggestion or motivation to combine the applied art and even assuming *arguendo*, that there was a suggestion to combine the art, there was no reasonable expectation of obtaining the claimed invention. Specific deficits were pointed out in the art, at least in Wu, Wagner and Goers and the combination of the art failed to remedy these defects. Further, contrary to the Examiner's assertions there was no reason to make the substitutions from the applied art as the Examiner suggested.

In the present Office Action beginning at page 3, last paragraph, the Examiner argues that:

> One of ordinary skill in the art at the time the invention was made would have been motivated to select and substitute T-cell specific antibodies or gp 120 (for the transferrin molecule of Wu *et al.* or Wagner *et al.*) as the targeting agents for protein-polycation conjugates or complexes of said conjugates additionally containing nucleic acids because such antibodies would allow for the specific direction and introduction of nucleic acid laden conjugates to T-cells for the purpose of introducing foreign DNA into the cells for either therapeutic purposes or for the production of interleukins (as is indicated by the Hirsch reference). From the

> teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants respectfully disagree.

Applicants have extensively argued against the combination of Wu or Wagner in view of Goers or Hirsch, Carriere and Knapp throughout the course of prosecution in the above-captioned application. All of these arguments are reiterated and incorporated herein by reference. The Examiner newly cites Young and Weinberger for the proposition that "T-cells transfected with gamma interferon or differentiation antigen encoding DNA express the interferon or differentiation antigen. Thus, one skilled in the art would have had a reasonable expectation of success in expression of genes transfected into T-cells." Regardless of the alleged teachings of Young and Weinberger this applied art still fails to remedy the deficit resulting from the combination of the remaining applied art, because there is still no suggestion to combine the art to obtain the claimed invention.

In the response filed May 27, 1997, Applicants submitted 6 pages of arguments in rebuttal of the Examiner's rejections. None of the arguments were rebutted or even specifically addressed. Rather at page 4, first full paragraph of the office action, the Examiner indicated that "Applicants' arguments have been considered but are not found persuasive for the following reasons . . ." The Examiner then proceeded to elaborate the rejection based on *Graham v. John Deere Co.*, 148 U.S.P.Q. (BNA) 459 (1966) .

Applicants acknowledge that *Graham* provides general guidance for analysis of the obviousness issue. *Graham*, however, does not provide the Examiner with a legal basis for

rebutting Applicants' previous arguments. In addition, *Graham* does not provide a basis for finding the claimed invention obvious in view of the applied art.

Specifically, Applicants raised the following issues in the response filed May 27, 1997:

> The Examiner draws the Applicants' attention to paragraph 1, column 2 of Wu "where it is explicitly taught that the invention is directed to the use of receptor mediated endocytosis to endow cell specificity to gene delivery." The Examiner correctly points out that the invention uses a "***ligand***-polycation-DNA complex" to achieve such delivery. However, other than a brief reference to antibodies at column 6, line 6 of Wu, the patent is almost completely drawn to the use of the asialoglycoprotein ligand as a so-called targeting mechanism for the DNA polycation complex.
>
> Additionally, Wu makes no specific reference to any "targeting agent" for use against cells of the T-cell lineage, as in the claimed invention. At best, there is no more than an indefinite suggestion to use ligands, e.g. antibodies, other than the asialoglycoprotein. In effect, this may disclose a potentially infinite genus of antibodies, although not the antibodies required for the claimed invention, i.e. those "capable of binding to a cell surface protein . . . expressed by cells of the T-cell lineage." Further, neither the claimed protein-polycation complex nor antibodies used in the claimed complex are *sufficiently similar* in structure to any complex or antibody specifically disclosed in Wu so as to render the claimed invention obvious. *In re Jones,* 21 U.S.P.Q.2d 1941, 1943 (Fed. Cir. 1992).
>
> Consistent with the above position is the more recent decision of *In re Baird,* 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994), which stated that "[a] disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a *preference* leading away from the claimed compounds." (Emphasis added). A single mention of antibodies can be said to represent a disclosure of "millions of compounds." Furthermore, Wu clearly exhibits a "preference leading away from the claimed compounds" at column 6, lines 3-5 where it recites, "*[t]ypically* glycoproteins having certain exposed terminal carbohydrate groups are used. . ." (Emphasis added). Thus, under both *Jones* and *Baird*, the claimed invention would fail to be rendered obvious in view of Wu, because Wu fails to *fairly* suggest such an invention.

(Response of May 27, 1997, page 3, last paragraph bridging to page 4, full page). If the rejection continues to be maintained, Applicants respectfully request the Examiner to specifically address these specific points.

Additionally, Applicants raised several issues beginning at page 5 of the May 27, 1997 response that have still not been addressed by the Examiner. Applicants against respectfully request the Examiner to address the following points:

The Examiner next states that "Wagner teache[s] the use of transferrin-polycation-DNA complexes to transfect cells, and while limited to 'transferrinfection' teaches that protein-polycation-DNA complexes were useful for delivery of DNA into cells." Applicants disagree with the broad generalization that the Examiner derives from Wagner. In particular, the Examiner's attention is drawn to Wagner at page 3414, right hand column where it is stated that "we have developed a DNA transferrinfection, in which we ***subvert*** a natural iron-uptake mechanism to transport DNA." Thus, Wagner indicates the mechanism by which he believes the DNA uptake occurs, i.e. subversion of the ***natural*** iron uptake mechanism. Clearly, such a mechanism must only apply to the use of transferrin and would not suggest a more general approach for targeting protein-polycation complexes as the Examiner contends. Nor can Wagner suggest the particular use of ligands for cell surface proteins of the T-cell lineage.

The Examiner next argues that in Goers "[t]he use of antibodies to deliver DNA and toxin into cells was well established at the time of the invention." Applicants respectfully suggest that this is irrelevant to the present issue, that is, whether there was the requisite suggestion to combine the art to arrive at the claimed invention. Merely because various antibodies were known to be internalized into a cell or that antibodies may have been used to deliver DNA, this does not mean that the requisite suggestion to combine the art as the Examiner has suggested was present.

In fact, it is not even clear to Applicants where Goers describes the use of antibodies to deliver DNA to the cell. The Examiner is respectfully requested to point out such a recitation. Rather, Goers appears to relate to the use of an antibody with a therapeutic agent conjugated thereto. In any event, this still fails

to provide the needed suggestion to render the claimed invention obvious.

> At page 4, line 18 of the response, the Examiner alleges that "the primary reference [Wu] is different from the claimed invention in ***only*** the targeting agent used to direct the DNA into a cell." While Applicants acknowledge that this is a deficit of the primary reference, the Examiner has overlooked the additional fact that the primary reference also fails to suggest the cell type i.e., the T-cell lineage for which the claimed protein-polycation conjugates are designed. Contrary to the claimed invention, the protein-polycation complex of Wu will presumably be taken up by any cell that has a transferrin receptor, thereby not being cell-type specific. As argued above, this again is no more than at best, an indefinite suggestion to make the claimed invention because of the myriad number of possible targeting agents suggested in Wu.

Applicants assert that the above issues are of significant consequence to the present rejection. These issues previously raised by Applicants clearly demonstrate the impropriety of the rejection which is based on a combination of the applied art. Additionally, as discussed above, the two primary references and at least one of the secondary references fails to support the Examiner's argument. Therefore the rejection should be withdrawn.

Further, Applicants respectfully suggest that the Examiner is using hindsight reconstruction to obtain the claimed invention. Such hindsight analysis has consistently been deemed inappropriate by the courts. The Examiner has done no more than use the Applicants' invention as a template and then picked and chosen elements from the art to fill any gaps. *In re Gorman* 18 U.S.P.Q.2d (BNA) 1885 (Fed. Cir. 1991).

Repeatedly, the Examiner raises the question of what the routineer would have recognized. Certainly if one starts with knowledge of the claimed invention, as has been done by the Examiner, then the question might become, would a routineer have known to make an appropriate substitution? The routineer, however, would *not* have had the advantage of knowing what the invention was. It is only after reading the application that such knowledge becomes

available. Therefore, it is more appropriate to begin the analysis with the question, "would the routineer looking at the applied art have a motivation to combine the art to obtain the claimed invention and even if the art was combined, would there be a reasonable expectation of obtaining the claimed invention? The answer to both questions is no.

The Examiner's new citation of Young fails to add anything to the previously applied combination of art. Young purportedly discusses stable transfection of T-cells. This, however, does not suggest the claimed invention when combining the applied art. Again, if one skilled in the art had no preconceived idea of the claimed invention and did nothing more than study the art that the Examiner cited, the combinations that such an individual might obtain from the art would be almost endless. Nothing in the art itself points to obtaining the protein-polycation complex of the claimed invention, i.e., one that is targeted for T-cells. Furthermore, nothing would lead to the specific types of conjugates as set forth in claims 11-16 or the protein-polycation/nucleic acid complex of claims 17-20 ro 36-40.

In the office action at page 5, second paragraph, the Examiner states that "[i]n the case of this invention, the routineer may be considered to be a Ph.D. or an M.D. . . *who practices in the DNA art as it relates to the transfection of cells with targeting constructs.*" (Emphasis added).

It is suggested that the Examiner has even more narrowly defined one of skill in the Office Action at page 2, end of paragraph 2, where it was stated that "[t]his relevant prior art relates to those persons engaged in *transfection of T-cells with antibody-polycation-DNA constructs.*" (Emphasis added.)

Applicants respectfully submit that the Examiner has, in effect, tailored the ordinary artisan to be the actual inventors of the claimed invention. This is an inappropriate approach.

Inventors are not necessarily those of *ordinary* skill in the art. The Federal Circuit has stated that:

> . . . one should not go about determining obviousness under § 103 by inquiring into what patentees (i.e. inventors) would have known or would likely have done, faced with the revelations of the references. A person of ordinary skill in the art is also presumed to be one who thinks along the line of *conventional wisdom* in the art and is *not* one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, it makes no difference which.

*Standard Oil Co. v. American Cyanamid Co.*, 227 U.S.P.Q. (BNA) 293, 298 (Fed. Cir. 1985). (Emphasis added).

Additionally, Applicants are not aware of any decision that so narrowly describes one of skill in the art, as the Examiner has done. If the Examiner is aware of such precedent, he is respectfully requested to provide the citation in the next Office Action. Generally, the ordinary artisan in the biotechnology arts is considered as having a certain level of education and perhaps experience in molecular biology or molecular genetics. In effect, the Examiner has begun with the claimed invention as a starting point and then described one of skill in the art as being one who already knows the invention.

In the Office Action at page 5, end of the page, the Examiner stated that one skilled in the art "would have recognized that transferrin and specific antibody were equivalents for the purpose of targeting DNA to cells, . . ." This is merely a conclusory statement and Applicants respectfully request the Examiner to provide support for this contention or an Examiner's affidavit under 37 C.F.R. § 1.107(b).

At page 5, the Examiner also refers to *Ruff and Dukeshire* 118 U.S.P.Q. 340 (CCPA 1958) to support the rejection based on what the Examiner alleges are equivalents, i.e. transferrin and specific antibodies, based on the alleged teachings of Wu. First, Applicants respectfully

request the Examiner to point out the specific teaching in Wu, that indicates that "*transferrin* and specific antibody were equivalents for the purposes of targeting DNA to cell" and that "antibodies may be used as targeting agents in the place of *transferrin*." (*See* Office Action at the bottom of page 5.) (Emphasis added.) Applicants have been unable to find either teaching. Second, Applicants previously argued that there is no structural homology between transferrin and specific antibodies (*See* Response of May 27, 1997 at page 7 third paragraph). Further, transferrin and antibodies are not necessarily "equivalents" and will not be viewed as such by one skilled in the art. Third, the conjugates to which the Examiner refers to in Hirsch, comprise a targeting agent directly attached to the DNA. Contrary to this, the claimed invention is a conjugate comprising the targeting agent (e.g. the antibody) directly attached to a polycation.

The Examiner cites *Ruff* for the proposition that "it is only where equivalency is known to prior art or obvious to one of ordinary skill in the art that substitution of one equivalent for another is not invention." (Office Action at page 5, last paragraph.) Applicants acknowledge this recitation in *Ruff* at page 346, right hand column, paragraph two. It is respectfully submitted, however, that the Examiner may have overlooked the end of the same paragraph that states, "[i]t will be found on examination that the equivalence which the applicants in these cases showed was not previously known in the art." As in *Ruff,* the same is true in the present application because nowhere has the Examiner shown that the art recognized the equivalence of "transferrin and specific antibodies" for targeting the protein-polycation complexes.

The citation of *Ruff* fails to provide support for the Examiner's rejection for several additional reasons. The issue in *Ruff* pertained to obviousness based on the substitution of compounds with structural similarity. No structural similarity between transferrin and the targeting antibodies has been established. Further in *Ruff*, the appellants were alleged to have

made an admission of equivalency based on the appellants own patent disclosure. Contrary to *Ruff,* the present Applicants have not made any admissions of equivalency between "transferrin" and other targeting agents for T-cells, nor has the Examiner provided any evidence of such equivalency. Therefore, *Ruff* does not support the Examiner's position.

Even assuming *arguendo,* that there is some indication of equivalency between transferrin and the targeting agent that can be found in the specification, under *Ruff* this is still insufficient for a finding of obviousness.

> That two things are *actually* equivalent, in the sense that they will both perform this same function, is not enough to bring into play the rule that when one of them is in the prior art the use of the other is obvious and cannot give rise to patentable invention.

*Id.* at 347. (Emphasis in original.) Thus, *Ruff* further fails to support the Examiner's argument.

Based on all the above, this rejection is overcome and should be withdrawn.

**C. Claim 17, 20, 28-29 and 32-34**

At page 6 of the Office Action, the Examiner has rejected claims 17, 20, 28-29 and 32-34 under 35 U.S.C. § 103 as allegedly being unpatentable over Wu or Wagner in view of Goers, Hirsch, Knapp and Carriere as applied in the previous rejection and further in view of Haseloff or Rossi and Applicants allegedly admitted prior art regarding oncogene inhibitory nucleic acids at page 26, paragraph 3 of the specification. Applicants respectfully traverse this rejection, incorporate by reference herein, reiterate and expand on the response filed May 27, 1997.

Applicants note that the Examiner did not introduce Young and Weinberger into this rejection as was done in the first rejection of the current Office Action. Applicants request clarification in this regard. If, however, Young and Weinberger are newly introduced in the next

Office Action the Examiner is requested not to make said action final in order to allow the Applicants to have adequate opportunity to respond to the new rejection.

Specifically, beginning at the bottom of page 6, the Examiner argues that:

> In view of the teachings of Rossi et al. and/or Haseloff et al., one of ordinary skill would have recognized that the targeting of ribozymes to T-cells expressing oncogene proteins or HIV proteins using polycation-protein conjugates such as those taught by Wagner et al. would have been useful for inactivation of the genetic transcripts contained within the cells. Further, one of ordinary skill would have recognized, prior to Applicant's earliest priority date, that the targeting specificity of the system disclosed by Wagner et al. could be greatly enhanced by the use of antibodies to specifically target therapeutic agents such as ribozymes.
>
> One of ordinary skill in the art at the time the invention was made would have been motivated to select and substitute T-cell specific antibodies or gp 120 (for the transferrin molecule of Wu et al. or Wagner et al.) as the targeting agents for protein-polycation conjugates or complexes of said conjugates additionally containing nucleic acids because such antibodies would allow for the specific direction and introduction of ribozyme laden conjugates to T-cells for the purpose of introducing foreign nucleic acids, such as ribozymes, into the cells for the inactivation of RNA contained with the cells. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was <u>prima facie</u> obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants respectfully disagree.

All of the arguments set forth in the preceding rejections concerning the cited art, apply equally well to this rejection and are reiterated herein. Applicants continue to maintain that the Examiner has set forth no suggestion or motivation for combining the art related to ribozymes with the additional applied art in an attempt to obtain the claimed invention.

The Examiner referred to reasons "set forth in paragraph 17 herein." It is not clear which paragraph the Examiner is referring to because there does not appear to be a paragraph 17 in the current Office Action. Applicants assume, however, that the Examiner is referring in general, to the arguments already made in the previous rejection. If Applicants' assumption is incorrect and there is a specific argument that the Examiner wishes to bring to Applicants' attention, the Examiner is requested to clarify this issue in the next Office Action.

At page 7, second full paragraph, the Examiner noted that :

> Applicant argues that there is no motivation to target ribozymes to T-cells based on the combination of references. The obviousness of the targeting agent-polycation conjugates have been discussed above. This rejection is based upon the additional element of ribozymes being recited in the claims. Ribozymes are a nucleic acid and one skilled in the art would have expected such ribozymes to be capable of association with the polycation-targeting agent conjugates produced in the previous rejection through the combination of references. One of ordinary skill in the art would have had a reasonable expectation of success in forming a protein (antibody)-polycation-ribozyme complex in view of the combination of references.

The beginning of the above paragraph does nothing more than reassert the arguments used in the previous rejections concerning the general combination of applied art. Applicants' previous arguments in rebuttal of the already addressed art are equally applicable to this rejection. It is still not clear to Applicants how the art suggests the use of a ribozyme in a protein-polycation conjugate. Again, the Examiner is doing nothing more than using the claimed invention as a template and then further using Rossi and/or Haseloff in an attempt to fill in missing gaps.

Further Applicants respectfully request the Examiner to answer the following points previously raised but unanswered, in the response filed May 27, 1997 (beginning at page 9):

Additionally, in the response filed August 28, 1996, Applicants attacked the use of both Haseloff and Rossi for failing to remedy the deficits of the initial combination of the art as well as for not providing either a motivation to combine the art or a reasonable expectation of successfully obtaining the claimed invention upon combination of the art. Applicants maintain this position.

Applicants continue to assert that the use of Haseloff and Rossi is nothing more than an attempt to add individual components previously missing from the combination of the art in order to arrive at the claimed invention. As has been repeatedly argued, such picking and choosing individual components without any suggestion to do so is an improper approach to the obviousness analysis.

The Examiner has set forth no suggestion for combining the art related to ribozymes with the additional applied art. Rather, the Examiner merely refers back to the previous rejection in this office action and argues that "the obviousness of the targeting agent-polycation conjugates have been discussed above". First, this does not address the suggestion to combine applied art. The Examiner has argued the "obviousness" of the invention, and not provided a suggestion to combine the art.

Second, Applicants contend that the Examiner's argument does not provide the requisite suggestion to substitute an antibody to a T-cell protein or the use of other proteins for what had been previously used in the art. Furthermore, the Examiner's argument even fails to suggest the replacement of a specific type of nucleic acid i.e., a ribozyme for nucleic acids in general. Applicants specifically request the Examiner to indicate why a ribozyme that has a specific function is an obvious substitution for nucleic acids in general, which at best is an indefinite suggestion.

Further, the Examiner makes no more than a conclusory argument that one of skill in the art would have a reasonable expectation of success "in forming a protein (antibody)-polycation-ribozyme complex in view of the combination of references." Applicants contend that merely referring to the combination of art as the basis for a reasonable expectation of success, does not support such an expectation. Therefore, Applicants request specific reasons why such a reasonable expectation of success exists in the applied art and further request specific citations from the art to support such an outcome.

Based on all the above this rejection should be withdrawn.

**D. Rejection of Claims 1 and 9-10**

At page 7 the Examiner rejected claims 1 and 9-10 under 35 U.S.C. § 103 as allegedly being unpatentable over Wu or Wagner in view of Goers and Knapp and Carriere as applied above, and further in view of Goding, Ghettie *et al., Molecular Immunol. 23*:1371 (hereinafter-Ghettie I), Ghettie *et al., Mol. Immunol. 25*:473 (hereinafter - Ghettie II) or Mota *et al., Immunol.* Letters (hereinafter Mota). Applicants respectfully traverse this rejection, incorporate by reference herein, reiterate and expand upon the Response filed May 27, 1997.

At page 8 of the Office Action, the Examiner referred to "[t]he teachings of the references have been discussed in paragraph 18. . ." It is not clear what paragraph the Examiner is referring to because there does not appear to be a paragraph 18 in the current Office Action. The Examiner is respectfully requested to clarify this issue in the next Office Action.

Specifically the Examiner argues that:

> One of ordinary skill in the art at the time the invention was made would have been motivated to select make [sic] an antibody-protein A-polycation compound because such proteins would have allowed for the specific direction and introduction of nucleic acid laden conjugates to T-cells or facilitated the isolation of such antibodies through ion exchange chromatography. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants respectfully disagree.

The arguments as they apply to the already rebutted portion of the combination of art apply equally well to this rejection. The Examiner indicates that the Applicants' previous arguments have not been found persuasive because "one of ordinary skill in the art would have

recognized that Protein A-polycation conjugates would have been an 'universal' reagent useful for the attachment of the DNA to IgG antibodies of any specificity." (Office Action at page 8, 3rd paragraph). It is respectfully suggested that this statement fails to answer Applicants' previous arguments in this regard.

Applicants draw the Examiners attention to page 11 of the response filed May 27, 1997 and respectfully request the Examiner to directly address the issues raised at this point. Applicants have argued against the Examiner's assertion that protein A-polycation conjugates would have been recognized as a universal reagent. Specifically Applicants argued that:

> All of the newly cited art relates to protein A-ricin conjugates, not protein-polycation conjugates for the attachment of DNA to IgG antibodies. Further, at least Ghettie I and Motta relate to the binding of the protein A-ricin conjugates to "antibody coated cells". This is clearly distinct from antibody-protein A-polycation conjugates. Additionally the reference to a "universal" reagent in Ghettie II, is to the "use of protein A-ricin toxin conjugate as a 'universal' specific toxin for the '*in vitro*' killing of various antibody-coated target cells," [not as a] (Ghettie II last two lines of the abstract), not as a "universal reagent useful for the attachment of DNA to IgG antibodies of any specificity." (Office Action at page 7, lines 11-12).
>
> Furthermore, in the last paragraph of Ghettie II (page 1378), they refer to the "universal" use of the protein A-toxin, "provided that a specific SpA reacting antitarget antibody is available." Such a requirement cannot imply use of protein A as a "universal reagent" as the Examiner researched.

These earlier arguments address the same argument currently being raised, i.e. the use of Protein A-polycation conjugates as an alleged "universal" reagent. The earlier arguments appear to have been overlooked in the current Office Action. These arguments overcome the Examiner's rejection. Based on all of the above, this rejection should be withdrawn.

Applicants request the reconsideration and reexamination of this application and the timely allowance of the pending claims. If there are any other fees due in connection with the filing of this response other than those already submitted, please charge the fees to our deposit account 19-0036. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should be charged to our deposit account. If the prosecution of this application and the allowance of the claims can be expedited in any manner by discussion with the undersigned the Examiner is requested to contact the undersigned at (202) 371-2589.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Lawrence B. Bugaisky

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Date: April 27, 1998

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